Remarks

Information Disclosure Statement

The references not previously considered are being resubmitted. It should be noted that resubmission of references is expensive and time consuming. The Patent Office should bear some of the burden in trying to locate and consider references within a timely fashion, not years after applicants have submitted them. Consideration of all references on their merits is requested.

Rejection Under 35 U.S.C. § 112, first paragraph, enablement

Claims 11-13, 19-22, and 44-50 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d

1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

The Examiner's attention is drawn to the Board of Appeals decision in the parent of this application, U.S.S.N. 08/265,428, which contains no more disclosure than the present application.

The Board begins on page 7 with a discussion of the legal requirements for enablement, noting that the standard is whether one of skill in the art is able to practice the claimed invention at the time the application was filed without undue experimentation, stating in relevant part:

"nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples", quoting from In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) . The Board then notes that the burden is on the *examiner* to provide a reasonable explanation of why the specification does not enable the claimed invention.

The examiner has failed to meet his legal burden. The rejection at pages 8-20 is nothing more than unsubstantiated argument. This is not permitted.

Applicants have demonstrated actual reduction to practice in the application as filed (1) isolation of a nucleotide molecule encoding SR-BI from a first species and (2) isolation of a nucleotide molecule encoding SR-BI from a second species. Applicants' Declaration under 37 C.F.R. 1.131 demonstrates that this information was sufficient to screen data bases to obtain sequence encoding the human analog. Accordingly, applicants have proven that they enable claims to the nucleotide molecule encoding SR-BI from multiple species, the examiner having provided no evidence that one skilled in the art would not expect to be able to isolate the homologous nucleotides molecules from any number of other representative widely divergent species.

The Examiner's attention is drawn to applicants' declaration under 37 C.F.R. 1.132 in support of enablement. These statements must be taken as evidence absent evidence, not mere conjecture or argument, to the contrary. The examiner has apparently ignored the explanation and evidence provided for how one can isolate a genomic DNA using a cDNA. It was routine to screen genomic libraries using cDNA hybridization probes at the time of filing the present application (see Exhibits 6-8, submitted with the declaration under 37 C.F.R. 1.132). The hybridization conditions such as temperature and salt concentration can be adjusted to decrease the stringency of the probe hybridization. A lower stringency condition would allow for a probe to bind sequences that were very similar but not identical to the cDNA probe. This would be ideal for screening genomic libraries from different species for homologous sequences. Additional proof of this is shown by reference to U.S. Patent No. 5,998,141 to Acton, which the Board cited in its decision in this case. cDNA encoding SR-BI, just as applicants describe in their application, was not only used to isolate the genomic DNA encoding SR-BI, but also polymorphic variations. See example 1, beginning at col. 32, line 54. See also col. 17, lines 8-38, stating that the same hybridization conditions were used, and can be used, to isolate genomic DNA encoding SR-BI from different species and including polymorphs or allelic variations. Accordingly, the examiner's statements to the contrary are simply wrong.

One of skill in the art would have known in 1994 how to make, or obtain, a human genomic library and synthesize a radiolabeled cDNA probe with routine experimentation. Probing nitrocellulose filters with the radiolabeled cDNA probe was already established and

widely used in the art. These techniques were established and used routinely for at least 10 years prior to the filing of this application.

The specification provides a clear and enabling disclosure of these methods. The previously submitted declaration under 37 C.F.R. 1.132 referred to specific passages in the specification wherein general methods using nucleic acid probes to isolate genomic DNA sequences *via* probing libraries (page 10, lines 2-20); using nucleic acid probes (page 25, lines 10-20); and making genomic libraries (paragraph bridging pages 34 and 35) are all described.

Furthermore, the specification provides sufficient guidance for one skilled in the art to make and use a functional scavenger receptor encoded by the nucleic acid molecule of claim 11. As dictated in claim 11, the receptor's functionality is centered on binding to 1) LDL, or 2) modified liproprotein having the characteristics of acetylated low density lipoprotein, in cell medium containing 10% serum. Applicants have clearly demonstrated that this is routine by expressing both cDNA's and showing the binding of the SR-BI encoded thereby, using standard binding assays. That is all that is legally required. Page 40, lines 14-16, states that one would *typically* screen for expression of *functional* receptor. Pages 16 and 17 describe well known methods used for measuring receptor binding (and uptake and degradation). Such methods were well described in references dating back to 1983 and 1991 (Krieger and Freeman; see lines 8 and 9 of page 16). The *in vitro* binding activity of SR-BI is shown in Figures 2A,B and C, 3A and 3B, 5, 6, and 7. The *in vitro* binding specificity is compared to CD36 in Figures 4A, B and 5. This in combination with the materials and methods described in the application are clearly

enabling to show the function of SR-BI. The *in vivo* function in the binding of cholesteryl esters in HDL is shown in Figure 8A, B and also described, and shown diagramatically in Figure 9.

The examiner's statements that the structure of SR-BI is not defined are absurd - the nucleotide sequence defines specific amino acid sequence. The structure of the protein encoded by this amino acid sequence is shown in Figure 1B. Moreover, the examiner's attention is drawn to the fact that the claims drawn to the protein, and variants thereof, have been allowed and issued as a U.S. Patent in the parent application.

The claims do not mention SEQ ID NO:4 or SEQ ID NO:8. The claims are directed to nucleic acid molecules encoding a functional scavenger receptor protein type BI. The terms "SEQ ID NO:4" and "SEQ ID NO:8" are nowhere to be found in the pending claims. The specification need not teach which specific amino acid substitutions, deletions or insertions to make in SEQ ID NOs:4 and 8. As stated above, the claims are directed to *nucleic acid molecules* encoding a functional scavenger receptor protein type BI. Moderately stringent hybridization conditions (at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule, which one of ordinary skill in the art would know would consist of SEQ ID NO:3 or SEQ ID NO:7, just as the examiner has noted) allows for some variation in the nucleic acid sequence. However, the extent of this variation is precluded by the fact that what is encoded must be a receptor that binds to LDL or modified lipoprotein under the conditions defined by the claim.

In quoting the M.P.E.P §2164.08(a), the Examiner appears to be confusing structure (means) and the stated property (function) in the present claims. SEQ ID NO:3 and SEQ ID NO:7 are the two structural means used in defining the claimed nucleic acid molecules. These structural means, coupled with the explicitly stated stringency conditions in combination with the encoded amino acid sequence have the defined function and structure shown in Figure 1B, are all that is required to properly define the claimed nucleic acid molecules. Applicant's have not incorporated into the claims any other "means". It is worthwhile to illustrate that the claimed nucleic acids bind to SEQ ID NO:3 or SEQ ID NO:7 by virtue of their chemical structure *which is complementary* to the chemical structure of the target sequence. Antigen is also bound by antibodies by virtue of their chemical structure which is complementary to the chemical structure of the antibodies. *The structure is not complementary in the sense that one strand of DNA binds to a complementary strand of DNA, but complementary in that the three dimensional structure as well as the chemical composition is complementary to the three dimensional structure and chemical composition of the target sequence.*

Claim 19 is dependent from claim 11. As such, it is necessary for the claimed molecule to hybridize to SEQ ID NO:3 and SEQ ID NO:7 under moderately stringent hybridization conditions. In view of the present specification and what was known in the art at the time of filing the present specification (as discussed in the foregoing paragraphs) one of ordinary skill would realize that trial and error experimentation is not a requisite for isolating the molecule of claim 11 or claim 19. Indeed, **applicants were able to use SEQ ID NO:3 or SEQ ID NO:7 to**

identify the human sequence from an available data base. The claims do not make reference to "non-rodent" species. The claims are not directed to particular species for isolation of the molecules. Either of SEQ ID NO:3 and SEQ ID NO:7 and an available library is all that is required, under moderately stringent conditions, to give structure to the claimed molecule.

In response to the Examiner's comments regarding P1-established libraries and cloning genes using cDNA, enclosed is a copy of Yang *et al.* (*Proc. Natl. Acad. Sci.* USA, Vol. 87, pp 7907-7911, 1990) clearly demonstrating that the technique of using recombinant phage for the purpose of library screening was well-established by 1990. Furthermore, Southern hybridization and restriction fragment length polymorphism (RFLP) analyses were commonly used techniques at the time of filing the present application (for example, see body of Yang *et al.*). Additionally submitted are two abstracts (Rouleau *et al.*, *Genomics*, **1989**, 4(1):1-6; and Ioannou *et al.*, *Nat. Genet.* **1994**,6(1):84-9), illustrating the use of recombinant phage libraries enriched for human chromosome 22 sequences for use in RFLP analysis and P1 vectors for introducing recombinant DNA into *E. coli*, respectively. Using cDNA to aid in cloning entire genes would not have been undue at the time of filing the present application. Furthermore, chromosomal walking was a routine method used to clone many genes at the time of filing the application. The *application* of each *well known* technique to the particular situation that the researcher has carved out for him-/herself was routine. The examiner has admitted that library screening using probes from cDNA was routine (see page 16 of the office action mailed on August 6, 2003).

With respect to administration of compounds to block binding, the examiner is invited to review the examples and graphs showing inhibition of binding to the SR-BI. It is believed these *actual examples* fully demonstrate the use of compounds to inhibit SR-BI binding as claimed.

Lastly, once one has the SR-BI protein and/or the DNA encoding SR-BI, from any species, it is possible to make antibodies to the protein or hybridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim 50); it can be used as a target in a screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48). None of these methods require any reagents not explicitly described and demonstrated in actual examples in the application.

Rejection Under 35 U.S.C. § 112, first paragraph, written description

Claims 11-13, 19-22, 44-50 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

Many of the arguments and evidence discussed above with respect to enablement is also applicable with respect to written description. Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it

pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991).

For many years the leading case for the written description requirement in the biotechnology and pharmaceutical arts was *Eli Lilly v. Univ. of Calif. Board of Regents*, in *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

The Federal Circuit has since held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002). This standard has been reviewed and clarified further in the decision of *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003).

The rejected claims are not drawn to specific nucleotide sequences; they define nucleotide sequences by virtue of hybridization to defined sequences, as well as by the amino acids which they encode that must form a structure as shown in Figure 1B, having the claimed activity. Applicants have provided the sequences to which the claimed nucleotides must hybridize, as well as the conditions, the three dimensional structure and the function. These features fully define the claimed nucleotide molecules. It is well established at this point that once one provides the structure and function, and has reduced to practice representative species of a genus, one has complied with the written description requirements for the genus.

Rejection Under 35 U.S.C. § 112, second paragraph, indefiniteness

Claims 11-13, 19-22, and 44-50 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

The Examiner's suggestions at page 7 of the Office Action mailed on August 6, 2003, have been noted but are not believed to be necessary. The standard is whether one skilled in the art would know what is defined by the claim. Clearly the examiner fully understands what is meant by the claims, as would others skilled in the art. The examiner's attention is drawn to the issued parent, also defining the nucleotide molecules in the same terms, as well as the Acton patent described above. Hundreds of other patents have also issued using the language now pending in this application. Accordingly, the claim language meets the requirements of 35 U.S.C. 112, second paragraph, as well as distinguishes the claimed polynucleotides from those encoding CD36.

With respect to the issue regarding whether the cDNA encoding SR-BI from two species is adequate to define the cDNA encoding SR-BI from other species, the examiner is referred to the foregoing discussion on enablement, and the previously submitted Declarations under 37 C.F.R. 1.131 and 1.132 (and as referred to, and discussed, above).

Rejections Under 35 U.S.C. § 102 and § 103

Claims 11, 13, 19, 20, and 22 were rejected under 35 U.S.C. § 102(a) as being anticipated by, or under and 35 U.S.C. § 103(a) as obvious over, *J. Biol. Chem.* 268(25)18929-18935 by Calvo *et al.* ("Calvo"). Applicants respectfully traverse this rejection.

i. Calvo fails to anticipate the claims

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

Calvo does not express the disclosed nucleotide molecules. Calvo does not identify the nucleotide molecule, Calvo does not identify the functional activity of the protein encoded by the nucleotide molecule, Calvo does not include an expression vector, and Calvo does not identify the conditions under which other SR-BI encoding molecules could be isolated. Therefore Calvo does not anticipate the claimed nucleotide molecules.

ii. 1.131 Declaration

Applicants have submitted a Declaration under 37 C.F.R. 1.131 which should remove Calvo as prior art. Applicants submitted laboratory notebook pages describing the partial nucleotide sequence of an isolated clone which applicant's used to conduct computerized sequence comparisons. These comparisons turned up sequences for LimpII and CD36 (CLA-1 was not in the databases at that time). As further described in the declaration under 37 C.F.R. 1.131, the entire nucleotide sequence was obtained and compared to the nucleotide sequence of CLA-1 after September 5, 1993. The declaration clearly demonstrates that applicants had the nucleotide molecules in hand, expressed and characterized prior to publication of Calvo. The declaration also clearly demonstrates that applicants conceived prior to Calvo and diligently reduced to practice the claimed human sequence.

37 C.F.R. § 1.131 states, in pertinent part,

> (a)(1) When any claim of an application . . . is rejected under 35 U.S.C. 102 (a) or (e), or 35 U.S.C. 103 based on . . . reference to . . . a printed publication, the inventor of the subject matter of the rejected claim . . . may submit an appropriate oath or declaration to overcome the . . . publication. The oath or declaration must include facts showing a completion of the invention in this country or in a NAFTA or WTO member country before . . . the date of the printed publication.

* * *

> (b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice . . . .

The Applicant need only provide evidence that reasonably gives rise to an inference that the invention was completed before the reference date, in order to constitute a *prima facie* showing. No corroboration is required since the application process is *ex parte*. A Rule 131 affidavit is sufficient when it demonstrates that the Applicant has prior "possession" of that part of the invention disclosed by the reference, as is the case when a reference discloses a species falling within a claim to its genus. *See* Donald S. Chisum, **Patents** § 3.08[1][b] (Matthew Bender & Co. 1996). Possession in this context is shown by demonstrating conception, reduction to practice, and diligence--each as normally required in determining the date of invention. *See In re Mulder*, 716 F.2d 1542 (Fed. Cir. 1983).

In *In re Stempel*, 241 F.2d 755 (C.C.P.A. 1957), the court held that Applicant's affidavit under Rule 131 was not required to show priority with respect to the claimed genus, but only to the species disclosed by the cited reference, in order to remove that reference as prior art. The claims, both genus and species, were drawn to chemical compounds. *Stempel* overcame the

anticipation rejection by showing reduction to practice, prior to the effective date of the reference, of a species of the invention within the generic claims.

In *In re Tanczyn,* 347 F.2d 830 (C.C.P.A. 1965), the court qualified *In re Stempel*, stating that the *Stempel* doctrine did not apply to *partial* possession of the invention, as distinguished from *total* possession of a species within a genus claim. The *Tanczyn* application "did not involve a genus-species relationship." Id. at 833.

In *In re Clarke,* 356 F.2d 987 (C.C.P.A. 1966), the court extended the *Stempel* doctrine to the situation at issue in this application, that is where the Applicant's Rule 131 affidavit shows possession that is *not* of the entire invention nor of the part of the invention disclosed by the reference. The *Clarke* court held that the affidavit is sufficient to remove a reference where the Applicant demonstrates possession of such "invention" as to make the entire claimed invention or the reference part obvious to one of ordinary skill in the art. The court stated,

> "[i]n an appropriate case an Applicant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference. . . . Thus, we think that in an appropriate case a single species could be sufficient to antedate indirectly a different species of a reference.".

The CCPA also has phrased the rule, "[w]hen that species of the generic invention which has been completed prior to the effective date of the reference would make obvious to one of ordinary skill in the art the species disclosed in the reference, the reference may be said to have been 'indirectly antedated.'" *In re Schaub*, 537 F.2d 509, 512 (C.C.P.A. 1976) (quoting *In re Ranier*, 390 F.2d 771, 773-74 (C.C.P.A. 1968)). The *Schaub* court stated that "[a]ppellants have made a *prima facie* case that the compound of the reference is obvious from the compounds which they have made prior to the date of the reference. Appellants' compound III is the next higher homolog of the reference compound II, . . ." Id. at 512-13.

There is little, if any, Federal Circuit case law on point. However, the rule established in *In re Clarke* apparently remains valid, as one somewhat recent, "unpublished" (i.e. not citable as precedent) case seems to indicate. In *In re Rozmus*, 928 F.2d 412, 1991 WL 17232 (Fed. Cir.), the court stated that "[a]lthough Rozmus' [Rule 131] declaration showed reduction to practice of only a species of the generic invention, that alone is not fatal to his claim. A declaration proving a species is also sufficient to show possession of 'variations and adaptations which would, at the same time, be obvious to one skilled in the art.'" (quoting *In re Spiller*, 500 F.2d 1170, 1178 n.5 (CCPA 1974)).

Other cases discussing priority but which do not involve Rule 131 have stated, "[p]riority as to a genus may . . . be shown by prior invention of a single species, but the genus will not be patentable to an Applicant unless he has generic support therefor." *In re Zletz*, 893 F.2d 319, 323 (Fed. Cir. 1989); *see also Hoffman v. Schoenwald* 15 U.S.P.Q.2d 1512, 1514 (Bd. Pat. App. &

Int'f 1990) ("Conception of a species within the genus constitutes conception of the genus for priority of invention purposes.").

As noted above, Calvo, et al. reported isolation of a cDNA encoding a member of the CD36 superfamily. The protein was not physically isolated nor was the cloned DNA expressed, much less expressed on the surface of cells and shown to be functional, although a small piece non-functional portion (the carboxyl terminal region including residues 365-409) was expressed as a chimeric protein (page 18930). The function of the protein was not known, although its resemblance to CD36/LimpII was recognized based on the predicted similarities in structure and the authors speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934).

As demonstrated repeatedly by Appellants and discussed above, CD36 and SR-BI are *not* the same proteins nor do they have the same binding activity.

The previously submitted Declaration under 37 C.F.R. §1.131, demonstrates that a cDNA and encoded protein defined by the claims in issue was conceived and reduced to practice prior to the publication of Calvo, et al.. Appellants cloned the gene, they expressed the protein, and they characterized the protein and showed its function, **prior to** Calvo's publication date.

The Examiner has stated that the Declaration under Rule 1.131 does not "demonstrate that the Applicant was in possession of the any information regarding a CLA-1 protein or CLA-1 gene from any animal other than hamster prior to the publication of Calvo et al." Appellants respectfully point out that this is not in fact true. Submitted with the Declaration is a printout

obtained from the search of six databases (PDP, Swissprot, PIR, SPupdate, Genpept, GPupdate). This printout indicates that the Rat LimpII gene and the CD36 gene were among the genes with the highest homology to SR-B1. While these genes have been shown to be members of a different families within the superfamily of CD36 scavenger receptors than the SR-B1 proteins of the present application, for one of ordinary skill in the art they presented a nexus between the species described in the Declaration of Krieger and Acton and the genus which would include the CLA-1 gene described in Calvo et al. The validity of these assertions is evidenced by the fact that the CLA-1 gene was isolated using primers derived from CD-36 and LIMP II, related but non-homologous proteins. Surely, the possession of the homolog of the CLA-1 protein, with the information that it fell within the CD-36 superfamily, is more information than Calvo et al. had when they cloned the CLA-1 gene, but not the homolog, from rat. The Applicants clearly were in possession of the genus of SR-B1 proteins and nucleic acid molecules that encode these proteins prior to the publication of Calvo.

iii. Non-obviousness

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Particularly relevant to the matters under consideration here are

the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, *the full field of the invention must be considered*: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.... Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted, emphasis added).

In *In re Dow Chemical*, a combination of three components forming an impact resistant rubber-based resin was not found to be obvious based upon art disclosing the individual components. The court noted that the record had shown that the claimed combination had previously been made, *but did not produce the product desired.* "That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later successful one.... Recognition of need, and difficulties encountered by those skilled in the field, are

classical indicia of unobviousness," *Id.* at 1531 (citations omitted). The Court found that none of the prior art cited by the Appellant and the PTO suggested that any process could be used successfully in this three-component system to produce the product having the desired properties. Further, the Court stated that evidence from an expert expressing skepticism as to the success of the claimed combination before these inventors proved him wrong should be considered. *Id.* at 1532.

As discussed above, the Krieger and Acton Declaration clearly shows that the Appellants were in possession of the cDNA and expressed protein prior to the date of Calvo et al. Therefore, Calvo et al. is antedated and not effective 35 U.S.C. § 103 art.

However, it cannot make obvious the genus where there was no expression of a protein, nor recognition of its properties.

Among the reasons that the Examiner has previously argued that it would be obvious to go from the Human CLA-1 gene described by Calvo et al. to the hamster homologue are: (1) CLA is described as being structurally analogous to LIMPII: (2) amino acid sequence were highly conserved between human and rat LIMPII; (3) the genes had sufficient similarity to permit the isolation of LIMPII; (4) an artisan would have concluded that any mammalian protein encoding CLA-1 would have been readily isolated by probing a DNA library, since the hamster, as well as rat, was routinely employed as a laboratory model for determining the physiological significance of proteins of human origin since the scope of human experimentation is obviously limited, (5) and there was knowledge that there was homology between humans and rodents at the time. These all seem to be reasons that support Applicants' claim that Calvo is removed by

their 131 Declaration! Applicants have demonstrated that they cloned and expressed the hamster gene encoding the claimed SR-BI proteins, and that the gene hybridizes to the murine gene, prior to publication by Calvo et al. Accordingly, Applicants conceived of and reduced to practice the claimed invention prior to Calvo et al. Therefore, the Declaration under 37 C.F.R. §1.131 should conclusively remove Calvo et al. as a reference, and the claims found patentable to Appellants.

Allowance of claims 11-15, 19-22, and 44-50 is respectfully solicited.

Respectfully submitted,

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Date: December 8, 2003

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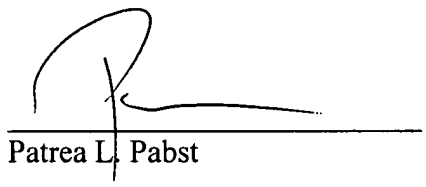
Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this Response to Office Action, and any documents referred to as to as being attached or enclosed, is being deposited with the United States Postal Service on this date, December 8, 2003, with sufficient postage as first-class mail in a box addressed to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.



Patrea L. Pabst

Date: December 8, 2003

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